interference between Kauffman and Horwitz go forward, because Pieczenik is directed to a different invention than Horwitz and Kauffman and moreover is only entitled to the 1991 filing date of a CIP;[1]

(2) Assuming the Examiner does not agree that Pieczenik is directed to a different invention than Kauffman and Horwitz, then an interference should be declared between all three, with Pieczenik only being accorded the 1991 filing date of the CIP, because this is the date that Pieczenik's invention was first enabled.

Furthermore, should the Examiner believe that the next course of action should be other than one of the above two alternatives, Applicants respectfully request a further opportunity to discuss this case with the Examiner, particularly in view of the many complex issues and number of papers filed in the present application.

Turning now to the Examiner Interview on April 14, 2000, the Examiner raised the following issues:

(i) After reviewing the Declaration by Phillip Patten, which was faxed to the Examiner prior to the interview and subsequently filed along with the Reply on April 14, 2000, the Examiner commented that the Declarant does not allege that using the lambda gt11 vector as described in Kauffman was *impossible*, which would allegedly mean that Pieczenik's

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[1] Even if the Examiner disagrees with Applicants' position that Pieczenik is only entitled to his 1991 filing date, Pieczenik should still be recognized as being directed to a different invention, and Applicants have in any event removed Pieczenik as a reference by means of the 131 Declaration previously filed on September 24, 1999.

random library of peptide epitopic sequences expressed by lambda gt11 could be matched to cognate antibodies as of Pieczenik's original filing date of August 28, 1985;

(ii) The Examiner also questioned whether Pieczenik might have provided a working example for the use of the lambda gt11 phage vector in Example II of U.S. Patent No. 5,866,363 (the '363 patent);

(iii) Even if Pieczenik fails to expressly teach how to identify random peptides within lambda plaques that also comprise *E. coli* proteins, the Examiner thought it might have been known in the art at the time of the Pieczenik 1985 filing date, as evidenced by the later publication of Ausubel (1990), to block antibody recognition of contaminating *E. coli* antigens in lambda plaques by treating antibody preparations with an extract of *E. coli* proteins prior to screening, and the skilled artisan allegedly would have combined such knowledge with the teachings of Pieczenik to enable the use of lytic lambda phage vectors to screen random peptide libraries;

(iv) Although the Declarant noted that affinity maturation is necessary for high affinity antibody binding, the Examiner is not convinced that naive antibody populations (isolated without immunization) are inoperable in view of Winger et al. (attached hereto). The Examiner also presented Abbas et al. (1991) to support his proposition that antibodies recognizing a given antigen and capable of binding to the antigen must be present in the primary repertoire even though affinity maturation has not yet occurred (allegedly supporting the operability of Pieczenik's naive antibody library in the absence of affinity maturation);

(v) If Pieczenik is not enabled as of August 28, 1985 for failing to disclose a filamentous phage vector system, then why do the same arguments do not apply to the instant application since neither discloses a filamentous phage vector system?

(vi) Despite the alleged lack of enablement of Pieczenik at the August 28, 1985 filing date, the Examiner is still of the opinion that Kauffman intended something less than random by the term "stochastic."

The following comments are responsive to the Examiner's concerns in the order they are listed above.

(1) Impossibility is not the standard for judging enablement

As summarized above, one of the Examiner's comments in response to the Patten Declaration was that Dr. Patten did not allege that identification of random peptide epitopes using a lambda gt11 library would be *impossible*, just that it would be very difficult. However, Applicants respectfully note that impossibility is not the standard for assessing enablement according to the Federal Circuit. Rather, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. U.S. v. Telectronics, Inc., 8 USPQ 2d 1217, 1223 (Fed. Cir. 1988) (with emphasis). Indeed, that some experimentation is necessary does not preclude enablement unless the amount of experimentation is unduly extensive. Utter v. Hiraga, 6 USPQ 2d 1709, 1714 (Fed. Cir. 1988); Telectronics, 8 USPQ 2d at 1222 (with emphasis).

The previous Declaration of Phillip Patten attached to the Reply filed April 14, 2000, appropriately conveys that the identification of peptide epitopes from a lambda gt11 library would require undue experimentation in light of the Pieczenik disclosure. In fact, Dr. Patten expressly states in paragraph (5) of the Declaration that "it would have been extremely difficult, if not impossible, to identify particular antibodies from a non-immunized animal that identify particular peptides within a randomly-generated population using a lytic phage expression system and the screening methods available in 1985" (with emphasis). As noted in paragraph (9) of the Declaration, although it might be feasible to identify specific clones that encode specific peptides *following immunization* with such peptides, it would take "a significant amount of screening" to identify peptides in a randomly generated population with antibodies isolated from an un-immunized mammal. As noted in paragraph (10) of the Declaration, "one would have much difficulty identifying interactions that are specific to cloned epitopes" due to the high background that would be encountered due to the presence of *E. coli* proteins and the lack of affinity maturation.

Nevertheless, in response to the Examiner's concerns as conveyed in the Interview on April 14, 2000, Applicants have provided a second Declaration by Dr. Patten. For this Declaration, Applicants' agent explained the meaning of undue experimentation as it is defined in the MPEP, and asked Dr. Patten to clarify whether the identification of random epitopes expressed in lambda gt11 libraries would require undue experimentation using antibodies from a mammal that had not been immunized. The second Patten Declaration is attached hereto,

and is believed to adequately convey the lack of enablement of the lambda gt11 library as conveyed in the Pieczenik disclosure.

(2) Example II of the Pieczenik '363 patent is not a "working" example because it is clearly prophetic

At the Examiner interview on April 14, 2000, the Examiner questioned Applicants' attack on Pieczenik's lambda gt11 expression system, noting that the Pieczenik '363 patent may contain a working example of the system. The Federal Circuit has verified that a "working example" contains experimental evidence. See Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, n.1 (1984). In this regard, MPEP § 608.01(p)(D)(5th ed. 1983) states:

> Simulated or predicted test results and prophetic examples (paper examples) are permitted in patent applications. Working examples correspond to work actually performed and may describe tests which have actually been conducted and results that were achieved. Paper examples describe the manner and process of making an embodiment of the invention which has not actually been conducted. Paper examples should not be represented as work actually done.

Furthermore, the Board has noted that, although the lack of working examples is not automatically indicative of lack of enablement, it "is, nevertheless a factor to be considered" in a case involving "an undeveloped art." See Ex parte Sudilovsky, 21 USPQ2d 1702, 1705 (BPAI 1992).

Using lambda gt11 vectors to express random peptide epitopes was an underdeveloped

art at the time of Pieczenik's first filing date, which was August 28, 1985. Using a naive library of antibodies to screen such an epitope library without prior immunization with an antigen of interest was also an underdeveloped art at that time. Accordingly, it is appropriate to question the enablement of the prophetic examples disclosed in Pieczenik, in light of the state of the art at the time.

Indeed, during the prosecution of the Pieczenik patent, the previous Examiner rejected the claims under 35 U.S.C. § 112, first paragraph, as failing to describe the expression of random oligonucleotides to produce peptides (Office Action dated June 29, 1992). In response to this rejection, Pieczenik pointed to Example IV as demonstrating the insertion of oligonucleotides into the minor coat protein gene III of bacteriophage f1, and Example V as teaching the expression of an exemplary oligonucleotide within the pIII minor coat protein and detection with antibody (see Exhibit H, excerpts from Pieczenik Amendments filed October 29, 1992, and May 15, 1992, attached to Reply filed September 24, 1999). Pieczenik identifies no other example or disclosure which would teach the expression of peptides in such a manner that they may be screened with antibodies in order to identify a particular peptide of interest. Only material added to the CIP disclosure is used to rebut the rejection.

In fact, George Pieczenik himself admits that he did not have evidence of the "operability of the invention" until he performed experiments with the filamentous phage system, as described in the Declaration of Pieczenik submitted with the Reply dated May 15, 1992 (Declaration was pursuant to 37 C.F.R. § 1.131; see p.7, second full paragraph, attached

as Exhibit I to the Reply filed September 24, 1999). There is significant evidence that he had not performed these experiments until after the grandparent application was filed. For instance, the Pieczenik Declaration was submitted along with others in order to antedate a prior art reference dated August, 1990, whereas no antedating Declarations were submitted in rebuttal to the Ballivet (Kauffman) reference, dated 1987.

If Pieczenik did have experimental evidence that the λgt11 system worked, he had the opportunity to submit it at the time he filed the 131 Declaration. Yet he only submitted data relevant to use of filamentous phage.

(3) It was not known in the art at the time of the Pieczenik 1985 filing date to block antibody recognition of contaminating *E. coli* antigens in lambda plaques by treating antibody preparations with an extract of *E. coli* proteins prior to screening

The Examiner presented the Ausubel reference as evidence that it might have been known in the art at the time of the Pieczenik 1985 filing date to block antibody recognition of contaminating *E. coli* antigens in lambda plaques by treating antibody preparations with an extract of *E. coli* proteins prior to screening for clones which express recombinant protein. As the Examiner recognized, Ausubel, however, was not available in 1985 because it was not published until 1990. However, the Examiner indicated during the interview that he nevertheless believes that the technology in Ausubel was being performed in 1985. Applicants have been unable to find references published at or before 1985 that evidence such a method,

therefore, if the Examiner has evidence that such techniques were available in 1985, it should be added to the record.

According to an art search performed by Applicants, the earliest evidence of the use of *E. coli* proteins to adsorb antibodies to *E. coli* to facilitate the recognition of cloned DNA was reported in Howell and Hargreaves (1988) (attached hereto), which reports the identification of *E. coli* transformants expressing antigenic determinants of *T. ovis* using infected sheep serum that had been adsorbed to remove *E. coli*-specific antibodies. However, it is pertinent to note that Howell and Hargreaves used antisera from sheep that were infected with *T. ovis*, and therefore likely had elevated levels of high affinity antibodies to *T. ovis* antigens. Moreover, Howell and Hargreaves was published three years after Pieczenik's parent application was filed.

Furthermore, Applicants' literature search suggests that an efficient process for obtaining a complete antibody repertoire specific for a complex mixture of *E. coli* proteins was not developed until the teachings of Anicetti et al. (1989), who showed that antibody reactivity to minor components in a mixture of *E. coli* proteins was not achieved until 112 days after immunization using a conventional protocol. The teachings of this reference suggest that, even if antisera to mixtures of *E. coli* proteins was available in 1985, it likely did not contain antibodies to all protein components. While this might not be fatal in a cloning procedure such as that of Howell and Hargreaves who seek to detect the expression of specific antigens using high affinity antisera from an infected animal, it will adversely affect how much screening and experimentation would be required to match any particular randomly-generated antibody to any

particular randomly expressed peptide in a mixture of minor *E. coli* components.

Lastly, it is worth noting that, even after antisera to *E. coli* proteins was available to facilitate immunoscreening of specific recombinant proteins using lytic lambda vectors, not one reference has since reported the use of a lytic lambda vector to express random peptide epitope libraries. An art search for epitope library in combination with a lambda vector revealed several references in the Medline database, four of which are attached hereto. All of the references where lambda was used to make epitope libraries concerned libraries comprising fragments generated from one cDNA of interest (not random fragments expressing every conceivable peptide of a defined length), and involved screening with distinct antibodies rather than a random library of naive antibodies.

(4) Neither Abbas et al. nor Winger et al. constitutes evidence that naive antibody populations may be used to screen random epitope libraries expressed using lambda gt11

The Examiner also questioned the Declarant's emphasis on the need for affinity maturation, given the discussion in Abbas et al. (1991) that "lymphocytes specific for different antigens develop before the introduction of antigens" (p. 70, first column), and given the showing in Winger et al. that antibodies isolated from a mammal that was not purposefully immunized could be selected that bound to specific antigens (see entire reference).

Applicants respectfully note, however, that Winger et al. does not discount the possibility that the animal used to isolate the antibody-producing cells had been previously

exposed to cross-reactive epitopes, hence the language "without prior *deliberate* immunization" (see title) and the reference to "(re)circulating" antibody producing precursors (see p. 4487, col. 2). Thus, the antibody-producing cells isolated in Winger et al. could in fact have undergone affinity maturation due to prior antigen *exposure*.

Moreover, even if naive antibody populations do exist in a mammal prior to deliberate immunization that recognize a given antigen as suggested by both Winger et al. and Abbas et al., it is not the presence of antibodies that might recognize a given antigenic peptide that Applicants dispute. Rather, Applicants question whether such antibodies can be matched to specific epitopes expressed in a random epitope library using a lytic phage expression vector. Indeed, Winger et al. conducted their screening experiments with whole antigens. As noted on page 4487, col. 2, "it is important to recognize, moreover, that each of the antigen systems described here constitutes a family of antigenic determinants rather than individual haptens" (with emphasis). Furthermore, Winger et al. readily admits at the bottom of col. 2 on page 4487 that the affinity of the antibodies generated without immunization may not compare to that of antibodies generated from immunized donors.

The fact that an antibody having low affinity for a given peptide might exist in a naive repertoire of antibody producing cells isolated from a non-immunized animal is irrelevant. Indeed, Dr. Patten points out in his Declaration that collections of hybridomas derived from naive mice were available in 1985 (see paragraph (11) of the first Patten Declaration). Rather, the pertinent question is whether such antibodies may be matched to particular cognate epitopes

existing in a vast library of peptides expressed in an environment of lysed cells in the presence of unblocked bacterial proteins and phage proteins, particularly given that such naive antibodies typically recognize more than one peptide (see the Patten Declaration, paragraph (8)).

In sum, the Examiner is correct to note that collections of hybridomas from naive animals may be screened to identify antibodies that bind to particular whole antigens. It is also correct to note that a random collection of peptides can be expressed using a lytic phage vector such as lambda gt11. However, is not reasonable to assume that such naive antibodies can be matched to any particular random peptide absent undue experimentation, particularly when no one, not even Pieczenik himself, has ever shown it can be done.

(5) The enablement issues pertaining to the lack of disclosure of a filamentous phage vector in the parent Pieczenik application are not applicable to Horwitz, because Horwitz enables other uses of a random population of nucleic acids or proteins

Applicants understand the Examiner's concerns with Applicants' §608 showing embodied in the Patten Declaration. Initially, Applicants would note that if the Examiner decides that Pieczenik is directed to a different invention, the Patten Declarations need not be considered. However, if Pieczenik is to be included in the interference, a decision must be made about its effective filing date, and the rules allow for the evidence that Applicants have presented.

According to MPEP 2308:

> Under 37 CFR 1.608, an applicant seeking to provoke an interference with a patent is required to submit evidence which demonstrates that the applicant is *prima facie* entitled to a judgment relative to the patentee. Evidence must be submitted when the effective filing date of the application is more than three months after the effective filing date of the patent. The evidence may relate to patentability and need not be restricted to priority, but if the evidence shows that the claims of the application are [also] not patentable, the claims in the application will be rejected (with emphasis).

Thus, the evidence presented herein and in previous papers are permissible evidence pursuant to 37 CFR 1.608, given the Examiner's suggestion that the Pieczenik '363 patent should be included in the requested interference.

As noted in the above-cited provision of the MPEP, and correctly raised by the Examiner during the interview on April 14, 2000, to go forward Applicants must show that their application does not suffer from the same enablement issues as the Pieczenik '363 patent due to failure to disclose the use of a filamentous phage vector. Applicants respectfully submit that Applicants' disclosure does not need to rely on the use of a filamentous phage vector system, because Applicants' invention is directed to a different goal than the invention of Pieczenik.

For instance, Pieczenik discloses no other use for his random peptide libraries than to use them as an epitope library to screen for cognate antibodies from a library of naive antibodies. In contrast, at no point does Horwitz mention this as a particular goal of the Horwitz invention. Rather, Horwitz are concerned with expressing random nucleic acids encoding random proteins, to identify random nucleic acids or proteins having a desirable

function. Such function need not be limited to binding to a cognate antibody. In fact, as described in the Horwitz application, such function can be in the form of a gene promoter (see paragraph bridging pages 1-2), a leader sequence or signal sequence (page 5, line 31), proteins that confer antibiotic resistance or resistance to toxins (page 7, lines 15-20), etc. Thus, the Horwitz invention seeks to identify random nucleic acids and proteins based on a wide variety of desired functional activities, none of which requires the use of a filamentous phage expression system.

Thus, the Horwitz claims are not subject to the same enablement issues as the claims of Pieczenik, because Pieczenik's application requires the use of a filamentous phage vector and Horwitz's does not. Because Pieczenik is not entitled to the filing date of his original parent application, Applicants have made a sufficient showing pursuant to 37 CFR 1.608 that they are *prima facie* entitled to a judgment relative to Pieczenik. Accordingly, Applicants respectfully request that the interference be allowed to go forward at this time.

(6) An interference should be declared between Kauffman and Horwitz, as both applications concern the screening of random nucleic acids and polypeptides for those having a desired biological activity

Separate and apart from Applicants' showing that Pieczenik is only entitled to a 1991 filing date, Applicants still believe that the interference is really only between Horwitz and Kauffman. It is Applicants' understanding, however, that the Examiner is still of the opinion

that Kauffman intended something less than random by the term "stochastic," and that Kauffman and Pieczenik are not directed to the same invention for that reason. Whatever the Examiner may decide about Pieczenik in regard to the request for interference,[2] Applicants respectfully submit that the Examiner must now recognize in view of all the evidence on record that Kauffman did in fact mean "random" by use of the term "stochastic," and an interference between Kauffman and Horwitz must go forward. In this regard, Applicants understand that the Kauffman file wrappers were not available to the Examiner when he previously determined that Kauffman's "stochastic" meant something different than random, and it is perfectly acceptable and understandable that a different decision now be made with all the evidence available.

For instance, as Applicants noted in the previous Reply to Examiner Interview filed September 24, 1999, Kauffman makes several statements during prosecution which make it clear that "stochastic" means or includes random. In the Response dated February 5, 1998, in the Kauffman '483 patent file history (Exhibit C attached to the Reply filed September 24, 1999), it is stated:

Applicants note that one could argue that Pieczenik does not belong in the interference for the same reasons that the present application does not suffer from the same enablement issues as Pieczenik. The applications are directed to different goals, and Pieczenik is a distinct species within the broader genus represented by Horwitz and Kauffman that is, with the exception of claim 7 because of lack of enablement, separately patentable as of its 1991 filing date (please refer again to section 2 of the Reply filed September 24, 1999).

> **Included in the definition of the term stochastic is random.** As is known to those of skill in the art, this term means that the claimed populations are random and as such are diverse. Diversity is an inherent outcome of the random polymerization of, for example, nucleotide or oligonucleotide building blocks as compared to the polymerization of a defined specific sequence.
>
> In light of the teachings within the application, the phrase "at least partially stochastic polynucleotide sequences" is intended to include sequences which are random, as described above. In addition, the phrase can include a sequence, part of which is stochastically generated, and part of which is not stochastically generated. The part that is not stochastically generated can be a known or unknown sequence. The phrase can additionally include a sequence that contains a biased amount of any one or all of the four nucleotide triphosphate or other building blocks which comprise the polynucleotide sequence. [See pages 17-18. Emphasis added.]

Likewise, in the Response filed August 23, 1995, for the '323 patent (Exhibit D attached to the Reply filed September 24, 1999), it is stated:

> **For example, included within the definition of the term 'stochastic' is random.** As is known to those skilled in the art, this term means that claimed populations are diverse. Diversity is an inherent outcome of the **random polymerization** of, for example, nucleotide or oligonucleotide building blocks as compared to the polymerization of a defined or specific sequence. [See pages 18-19. Emphasis added.]

Similarly, in the Response filed June 10, 1996, for the '514 patent (Exhibit E, p. 13, attached to the Reply filed September 24, 1999), Kauffman states in responding to a prior art rejection:

> [S]uch methods do not result in or suggest the production of **random, stochastic sequences as claimed in this invention.** General knowledge at the time of the invention did not teach or suggest the production of such **random, stochastic**

sequences. [Emphasis added.]

Thus, it abundantly clear that Kauffman's term "stochastic" includes random sequences given the comments that Kauffman himself makes during prosecution. Applicants respectfully remind the Examiner again that the Federal Circuit has directed the PTO to give claims their "broadest reasonable interpretation" during prosecution. *In re Morris*, 127 F.3d 1048 (Fed. Cir. 1997) (*citing In re Prater,* 56 C.C.P.A. 1381, 415 F.2d 1393, 1404-05, 162 U.S.P.Q. (BNA) 541, 550-51 (CCPA 1969). It follows that "[l]imiting claims . . . to what is described in the specification . . . would conflict with this practice," and that the prosecution file history should also be considered in construing the claims. *In re Morris*, 127 F.3d at 1055.

Furthermore, it is also apparent from other comments made in the file history of the Kauffman patents that Kauffman defines "random" in a similar manner to Applicants. In the present invention, a "random" nucleotide sequence is formed "without regard to a wild type sequence" (see, for instance, claim 3, and the specification at page 8, lines 11-19 and at page 28, lines 1-4). Likewise, in the file history for Kauffman patent '514, in the Response dated June 10, 1996 (Exhibit E, p. 16), it is stated:

> None of the cited art or general knowledge contains any specific suggestion to create stochastic sequences independent of "target sequences."

Similarly, in the Response dated May 24, 1996, for the '483 patent (Exhibit F, at pages 7-8,

attached to the Reply filed September 24, 1999), it is stated:

> **Sirotkin is directed to the mutagenesis of a known target DNA.** The mutagenesis methods described by Sirotkin result in a single randomly-located region in the target DNA with random substitute mutations. This mutagenesis is accomplished by adding two noncomplementary nucleotides to a primer and then incorporating these nucleotides into the template strand.
>
> **Applicants claim a process comprising the production of a population of stochastic or partially stochastic polynucleotide sequences.** Such populations are diverse in sequence and complexity and are produced by, for example, the random copolymerization or chemical coupling of nucleotide monomers. **Applicants claimed method does not utilize a template molecule nor does it result in substitution mutations within a single randomly located region within the target DNA.** [Emphasis added.]

Thus, not only does Kauffman describe the use of stochastically generated nucleotide sequences which are random in nature, it is clear that Kauffman uses the term "random" in the same manner as Applicants; that is, to refer to a sequence generated without regard to a wild type sequence. Accordingly, it is Applicants' belief that Kauffman and the present application disclose and claim the same invention, and that an Interference should be declared between the Kauffman patents and applications and the present application.

In summary, this Reply is believed to address all the issues raised in the second Examiner Interview. As a result it is clear that (1) an Interference between Kauffman and the present application should go forward because Kauffman and the present application describe the same patentable invention; and (2) although Applicants believe that Pieczenik should not be

added to the Interference because Pieczenik is directed to a separately patentable species within the genus claimed in the present application and Kauffman, even if the Examiner decides to include Pieczenik, Applicants have made the requisite showing pursuant to 37 CFR 1.608 that Applicants are entitled to a judgment relative to Pieczenik such that the interference should go forward with Piecznik only being given the benefit of a 1991 filing date.

To reiterate, only one of two options is now possible:

(1) The first option is that Pieczenik be removed from the present analysis and an interference between Kauffman and Horwitz go forward, because Pieczenik is directed to a different invention than Horwitz and Kauffman and moreover is only entitled to the 1991 filing date of the CIP; or

(2) Assuming the Examiner does not agree that Pieczenik is directed to a different invention than Kauffman and Horwitz, then an interference should be declared between all three, with Pieczenik only being entitled to the 1991 filing date of the CIP, because this is the date that Pieczenik's invention was first enabled.

Furthermore, should the Examiner believe that the next course of action should be other than one of the above two alternatives, Applicants respectfully request a further opportunity to discuss this case with the Examiner, particularly in view of the many complex issues and number of papers filed in the present application. Of course, if the Examiner wishes to discuss these issues further, he should feel free to contact the undersigned. Again, Applicants would be more than happy to assist the Examiner in any way possible such that the

Interference between Kauffman and the present application may be expedited.

Respectfully submitted,

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